PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
4239-55911		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/US 00/ 26689	29/09/2000	02/10/1999
Applicant		
THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-26, 37-41 and 27-32, as far as they refer to an invivo method, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 33-36 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Present claims 1-5, 17, 20-21, 23, 25-26, 33-38 relate to a compound defined by reference to a desirable characteristic or property, namely modulation of FGF-5 expression/activity or modulation of immune response to FGF-5.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the the use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunorecative sensitezed T cells sensitized with FGF-5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 00/26689

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/18 C07K14/50 A61K39/395 C07K16/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 24756 A (HUNAN GENOME SCIENCES INC.) 4 May 2000 (2000-05-04) claims 1-23 ---	1-41
X,P	WO 99 55861 A (EISAI CO. LTD.) 4 November 1999 (1999-11-04) claims 1-19,23,24 page 42, line 10 - line 3 page 46, line 20 -page 47, line 26 ---	1-5, 9-14,23, 24, 27-32, 37-40
X	WO 90 12597 A (THE SALK INSTITUTE FOR BIOLO) 1 November 1990 (1990-11-01) the whole document --- -/--	1-6,23, 24,37-39

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2001	20/07/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax. (+31-70) 340-3016	Siatou, E

1

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 05, 30 April 1998 (1998-04-30) & JP 10 017599 A (POLA CHEM IND INC), 20 January 1998 (1998-01-20) abstract	33-36
A	ZHAN X ET AL: "THE HUMAN FGF-5 ONCOGENE ENCODES A NOVEL PROTEIN RELATED TO FIBROBLAST GROWTH FACTORS" MOLECULAR AND CELLULAR BIOLOGY,US,WASHINGTON, DC, vol. 8, no. 8, 1 August 1988 (1988-08-01), pages 3487-3495, XP002034597 ISSN: 0270-7306 abstract	1-41
A	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; YAMANAKA K. ET AL: "Expression of fibroblast growth factors in human non-papillary renal cell carcinoma: Correlation with tumor progression." retrieved from STN Database accession no. 1999207619 XP002171451 abstract & INTERNATIONAL JOURNAL OF CLINICAL ONCOLOGY, (1999) 4/2 (74-77). ,	1-41
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YOSHIMURA, KOJI ET AL: "Messenger ribonucleic acids for fibroblast growth factors and their receptor in bladder and renal cell carcinoma cell lines" retrieved from STN Database accession no. 124:339650 HCA XP002171452 abstract & CANCER LETT. (SHANNON, IREL.) (1996), 103(1), 91-7 ,	1-41

-/--

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WERNER, SABINE ET AL: "Fibroblast growth factor 5 proto-oncogene is expressed in normal human fibroblasts and induced by serum growth factors" retrieved from STN Database accession no. 116:35063 HCA XP002171453 abstract & ONCOGENE (1991), 6(11), 2137-44 , -----	1-41

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 00/26689

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0024756 A	04-05-2000	AU 4688499 A	15-05-2000
WO 9955861 A	04-11-1999	AU 3170499 A	16-11-1999
WO 9012597 A	01-11-1990	US 5191067 A	02-03-1993
		CA 2053275 A,C	28-10-1990
		DE 69010330 D	04-08-1994
		DE 69010330 T	20-10-1994
		EP 0470183 A	12-02-1992
		JP 2891306 B	17-05-1999
		JP 4507093 T	10-12-1992
		US 5576288 A	19-11-1996
		US 5679637 A	21-10-1997
JP 10017599 A	20-01-1998	NONE	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13620

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

Please See Extra Sheet.

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
1-12, 14-16

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/13620

BOX II. OBSERVATIONS WHERE UNITY OF INVENTION WAS LACKING
This ISA found multiple inventions as follows:

This application contains the following inventions or groups of inventions which are not so linked as to form a single inventive concept under PCT Rule 13.1. In order for all inventions to be searched, the appropriate additional search fees must be paid.

Group I, claims 1-12 and 14-16, drawn to nucleic acid, vector, host cell, polypeptide, methods of making host cell and polypeptide.
Group II, claim 13, drawn to an antibody.
Group III, claim 17, drawn to a method of administering a polypeptide.
Group IV, claim 18, drawn to a method of diagnosis relating to mutations in DNA.
Group V, claim 19, drawn to a method of diagnosis relating to the expression of a polypeptide.
Group VI, claim 20, drawn to a method for identifying binding partners for a polypeptide.
Group VII, claims 21, 22 and 23, drawn to a method for identifying compounds which modulate the cellular response induced by FGFR5.

The inventions listed as Groups I-VII do not relate to a single inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: This Authority considers that the main invention in the instant application comprises the first-recited product, polynucleotide encoding FGFR5, and the first-recited method of using that product, namely in the process of producing the encoded polypeptide. Note that there is no method of making the polynucleotide. Also included in this group is the product made, namely the encoded polypeptide, and vector and host cell comprising the polynucleotide. Further, the ISA/US considers that the materially and functionally dissimilar product of group II and the additional methods of groups III-VII do not correspond to the main invention. This Authority therefore considers that the several inventions do not share a special technical feature within the meaning of PCT Rule 13.2 and thus do not relate to a single general inventive concept within the meaning of PCT Rule 13.1.

BNSDOCID <WO 0024756A1 | >

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1   GACCCCAGGTCCCGACAGCCCGAGATGACGCCGAGCCCCCTGTTGCTGCTCCTGCTGCCG   60
1                          M  T  P  S  P  L  L  L  L  L  P          12

61  CCGCTGCTGCTGGGGGCCTTCCCACCGGCCGCCGCCGCCGAGGCCCCCCAAAGATGGCC  120
13  P  L  L  L  G  A  F  P  P  A  A  A  A  R  G  P  P  K  M  A    32

121 GACAAGGTGCTCCCACGGCAGGTGGCCCGGCTGGGCCGCACTGTGCGGCTGCAGTGCCCA  180
33  D  K  V  V  P  R  Q  V  A  R  L  G  R  T  V  R  L  Q  C  P    52

181 GTGGAGGGGGACCCCGCCGCCCTGACCATGTGGACCAAGGATGGCCGCACCATCCACAGC  240
53  V  E  G  D  P  P  P  L  T  M  W  T  K  D  G  R  T  I  H  S    72

241 GGCTGGAGCCGCTTCCGCGTGCTGCCGCAGGGGCTGAAGGTGAAGCAGGTGGAGCGGGAG  300
73  G  W  S  R  F  R  V  L  P  Q  G  L  K  V  K  Q  V  E  R  E    92

301 GATGCCGGCGTGTACGTGTGCAAGGCCACCAACGGCTTCGGCAGCCTTAGCGTCAACTAC  360
93  D  A  G  V  Y  V  C  K  A  T  N  G  F  G  S  L  S  V  N  Y   112

361 ACCCTCGTGGTGCTGGATGACATTAGCCCAGGGAAGGAGAGCCTGGGGCCCGACAGCTCC  420
113 T  L  V  V  L  D  D  I  S  P  G  K  E  S  L  G  P  D  S  S   132

421 TCTGGGGGTCAAGAGGACCCCGCCAGCCAGCAGTGGGCACGACCGCGCTTCACACAGCCC  480
133 S  G  G  Q  E  D  P  A  S  Q  Q  W  A  R  P  R  F  T  Q  P   152

481 TCCAAGATGAGGCGCCGGGTGATCGCACGGCCCGTGGGTAGCTCCGTGCCGCTCAAGTGC  540
153 S  K  M  R  R  R  V  I  A  R  P  V  G  S  S  V  R  L  K  C   172

541 GTGGCCAGCGGGCACCCTCGGCCCGACATCACGTGGATGAAGGACGACCAGGCCTTGACG  600
173 V  A  S  G  H  P  R  P  D  I  T  W  M  K  D  D  Q  A  L  T   192

601 CGCCCAGAGGCCGCTGAGCCCAGGAAGAAGAAGTGGACACTGAGCCTGAAGAACCTGCGG  660
193 R  P  E  A  A  E  P  R  K  K  K  W  T  L  S  L  K  N  L  R   212

661 CCGGAGGACAGCGGCAAATACACCTGCCGCGTGTCGAACCGCGCGGGCGCCATCAACGCC  720
213 P  E  D  S  G  K  Y  T  C  R  V  S  N  R  A  G  A  I  N  A   232

721 ACCTACAAGGTGGATGTGATCCAGCGGACCCGTTCCAAGCCCGTGCTCACAGGCACGCAC  780
233 T  Y  K  V  D  V  I  Q  R  T  R  S  K  P  V  L  T  G  T  H   252

781 CCCGTGAACACGACGGTGGACTTCGGGGGGACCACGTCCTTCCAGTGCAAGGTGCGCAGC  840
253 P  V  N  T  T  V  D  F  G  G  T  T  S  F  Q  C  K  V  R  S   272

841 GACGTGAAGCCGGTGATCCAGTGGCTGAAGCGCGTGGAGTACGGCGCCGAGGGCCGCCAC  900
273 D  V  K  P  V  I  Q  W  L  K  R  V  E  Y  G  A  E  G  R  H   292

901 AACTCCACCATCGATGTGGGCGGCCAGAAGTTTGTGGTGCTGCCCACGGGTGACGTGTGG  960
293 N  S  T  I  D  V  G  G  Q  K  F  V  V  L  P  T  G  D  V  W   312
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FIG. 1A

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961  TCGCGGCCCGACCGCTCCTACCTCAATAAGCTGCTCATCACCGGTGCCCGCCAGGACGAT 1020
313  S  R  P  D  G  S  Y  L  N  K  L  L  I  T  R  A  R  Q  Q  D    332

1021 GCGGGCATGTACATCTGCCTTGGCGCCAACACCATGGGCTACAGCTTCCGCAGCGCCTTC 1080
333  A  G  M  Y  I  C  L  G  A  N  T  M  G  Y  S  F  R  S  A  F    352

1081 CTCACCGTGCTGCCAGACCCAAAACCGCAAGGGCCACCTGTGGCCTCCTCGTCCTCGGCC 1140
353  L  T  V  L  P  D  P  K  P  Q  G  P  P  V  A  S  S  S  S  A    372

1141 ACTAGCCTGCCGTGGCCCCGTGGTCATCGGCATCCCAGCCGCCGCTCTCTTCATCCTGGGC 1200
373  T  S  L  P  W  P  V  V  I  G  I  P  A  G  A  V  F  I  L  G    392

1201 ACCCTGCTCCTGTGGCTTTGCCAGGCCCAGAAGAAGCCGTGCACCCCCGCGGCTGCCCCT 1260
393  T  L  L  L  W  L  C  Q  A  Q  K  K  P  C  T  P  A  P  A  P    412

1261 CCCCTGCCTGGGCACCGCCCCGCCGGGGACGGCCCTCGACCGCAGCCGGAGACAAGGACCTT 1320
413  P  L  P  G  H  R  P  P  G  T  A  L  D  R  S  G  D  K  D  L    432

1321 CCCTCGTTGGCCGCCCTCAGCGCTGGCCCTGGTGTGGGGCTGTGTGAGGAGCATGGGTCT 1380
433  P  S  L  A  A  L  S  A  G  P  G  V  G  L  C  E  E  H  G  S    452

1381 CCGGCAGCCCCCCAGCACTTACTGGGCCCAGGCCCAGTTGCTGGCCCTAAGTTGTACCCC 1440
453  P  A  A  P  Q  H  L  L  G  P  G  P  V  A  G  P  K  L  Y  P    472

1441 AAACTCTACACAGACATCCACACACACACACACACACACTCTCACACACACTCACACGTG 1500
473  K  L  Y  T  D  I  H  T  H  T  H  T  H  S  H  T  H  S  H  V    492

1501 GAGGGCAAGGTCCACCAGCACATCCACTATCAGTGCTAGACGGCACCGTATCTGCAGTGC 1560
493  E  G  K  V  H  Q  H  I  H  Y  Q  C  *                        505

1561 GCACGGGGGGGCCGGCCAGACAGGCAGACTGCGAGGATGGAGGACCGAGCTCCAGACGAA 1620

1621 GGCAGGGGACCCATGGCGAGGAGGAATGGCCAGCACCCCAGGCAGTCTGTGTGTGAGGCA 1680

1681 TAGCCCCTGGACACACACACACAGACACACACACTACCTGGATGCATGTATGCACACACA 1740

1741 TGCGCGCACACGTGCTCCCTGAAGGCACACGTAGGCACACACGCACATGCACAGATATGC 1800

1801 CGCCTGGGCACACAGATAAGCTGCCCAAATGCACGCACACGCACAGAGACATGCCAGAAC 1860

1861 ATACAAGGACATGCTGCCTGAACATACACACGCACACCCATGCGCAGATGTGCTGCCTCG 1920
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FIG. 1B

BNSDOCID <WO 0024756A1T1 >

1921 ACACACACACACACGGATATGCTGTCTGGACGCACACACGTCCAGATATGGTATCCGG 1980

1981 ACACACACGTGCACAGATATGCTGCCTGGACACACAGATAATGCTGCCTTGACACACACA 2040

2041 TGCACGGATATTGCCTGGACACACACACACACGCGTGCACAGATATGCTGTCTGGACA 2100

2101 GGCACACACATGCAGATATGCTGCCTGGACACACACTTCCAGACACACGTGCACAGGCGC 2160

2161 AGATATGCTGCCTGGACACACGCAGATATGCTGTCTAGTCACACACACACGCAGACATGC 2220

2221 TGTCCGGACACACACACGCATGCACAGATATGCTGTCCGGACACACACACGCACGCAGAT 2280

2281 ATGCTGCCTGGACACACACACAGATAATGCTGCCTCAACACTCACACACGTGCAGATATT 2340

2341 GCCTGGACACACACATGTGCACAGATATGCTGTCTGGACATGCACACACGTGCAGATATG 2400

2401 CTGTCCGGATACACACGCACGCACACATGCAGATATCCTGCCTGGGCACACACTTCCGGA 2460

2461 CACACATGCACACACAGGTGCAGATATGCTGCCTGGACACACGCAGACTGACGTGCTTTT 2520

2521 GGGAGGGTGTGCCGTGAAGCCTGCAGTACGTGTGCCGTGAGGCTCATAGTTGATGAGGGA 2580

2581 CTTTGCCTGCTCCACCGTCACTCGCCCCAACTCTGCCCGCCTCTGTCCCCGCCTCAGTCCC 2640

2641 CGCCTCCATCCCCGCCTCTGTCCCCTGGCCTTGGCGGCTATTTTTGCCACCTGCCTTGGG 2700

2701 TGCCCAGGAGTCCCCTACTGCTGTGGCTGGGGTTGGGGGCACAGCAGCCCCAAGCCTGA 2760

2761 GAGGCTGGAGCCCATGGCTAGTGGCTCATCCCCACTGCATTCTCCCCCTGACACAGAGAA 2820

2821 GGGGCCTTGGTATTTATATTTAAGAAATGAAGATAATATTAATAATGATGGAAGGAAGAC 2880

2881 TGGGTTGCAGGGACTGTGGTCTCTCCTGGGGCCGGGACCGGCCTGGTCTTTCAGCCATG 2940

2941 CTGATGACGACACCCCGTCCAGGCCAGACACCACCCCCCACCCCACTGTCGTGGTGGCCC 3000

3001 CAGATCTCTGTAATTTTATGTAGAGTTTGAGCTGAAGCCCCGTATATTTAATTTATTTTG 3060

3061 TTAAACATGAAAGTGCATCCTTTCCCTCCAAAAAAAAAAAAAAAAAAAAAAA 3112

FIG. 1C

BNSDOCID <WO 0024756A1 >

SUBSTITUTE SHEET (RULE 26)

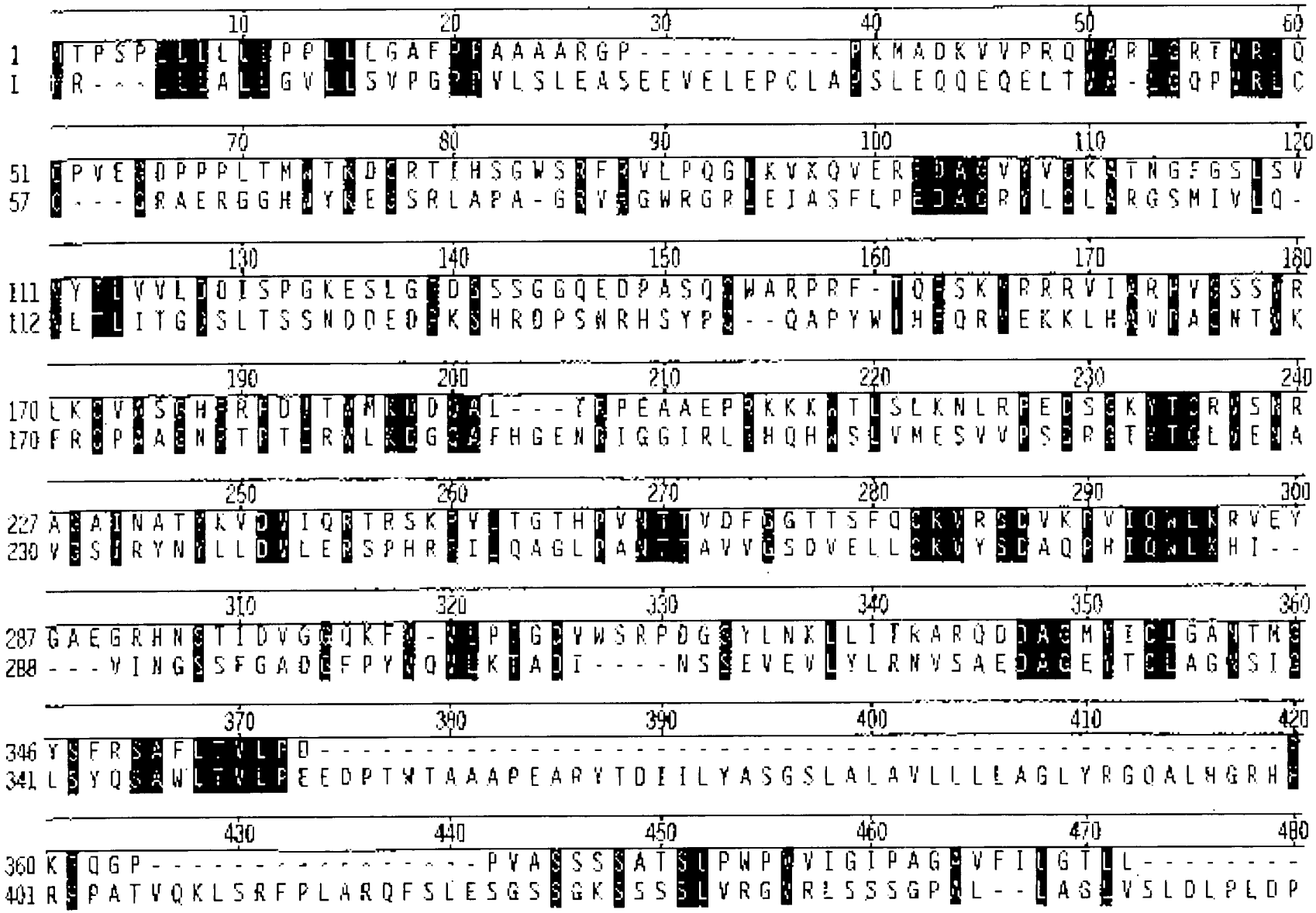

FIG. 2A

CORRECTED SHEET (RULE 26)

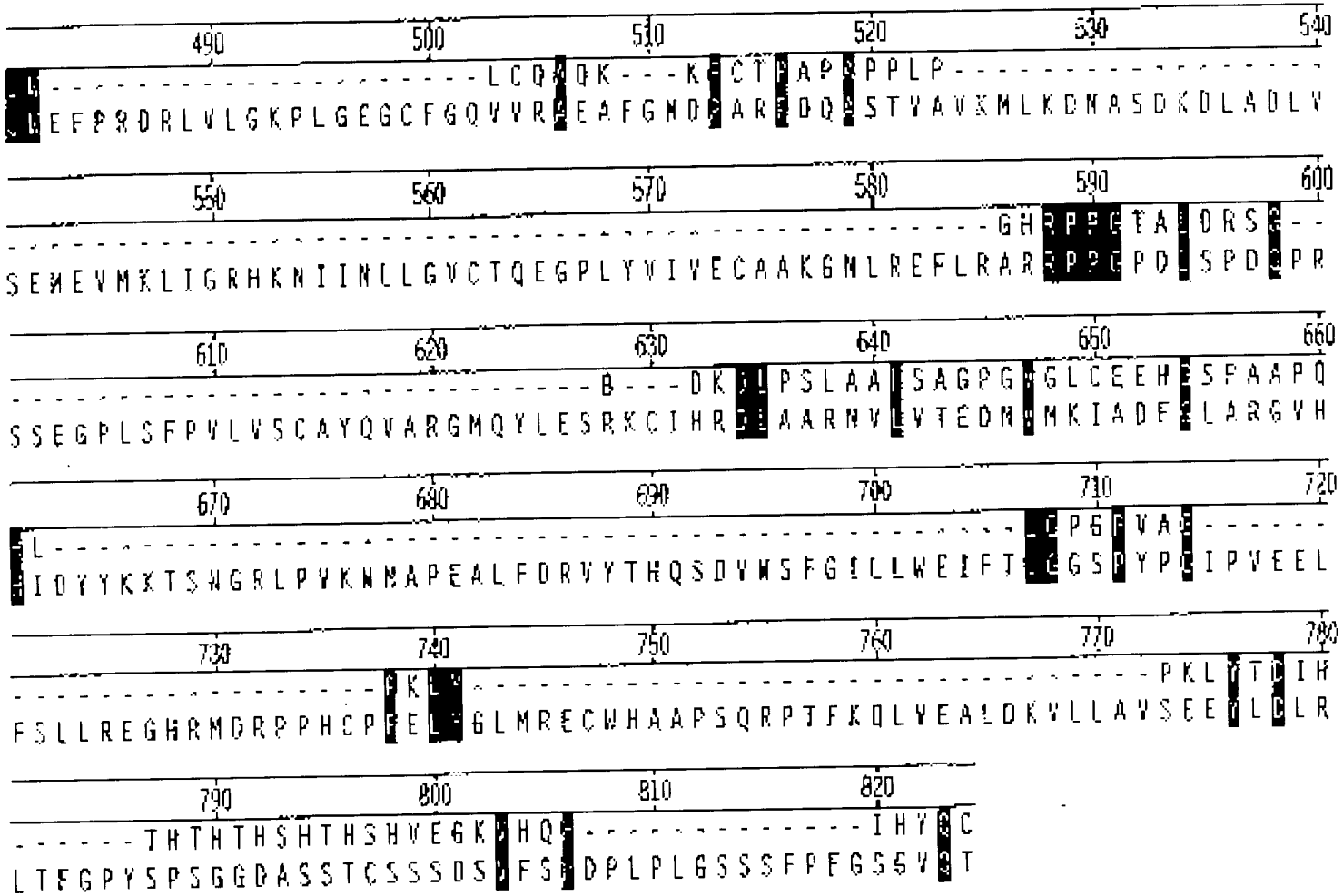

FIG. 2B

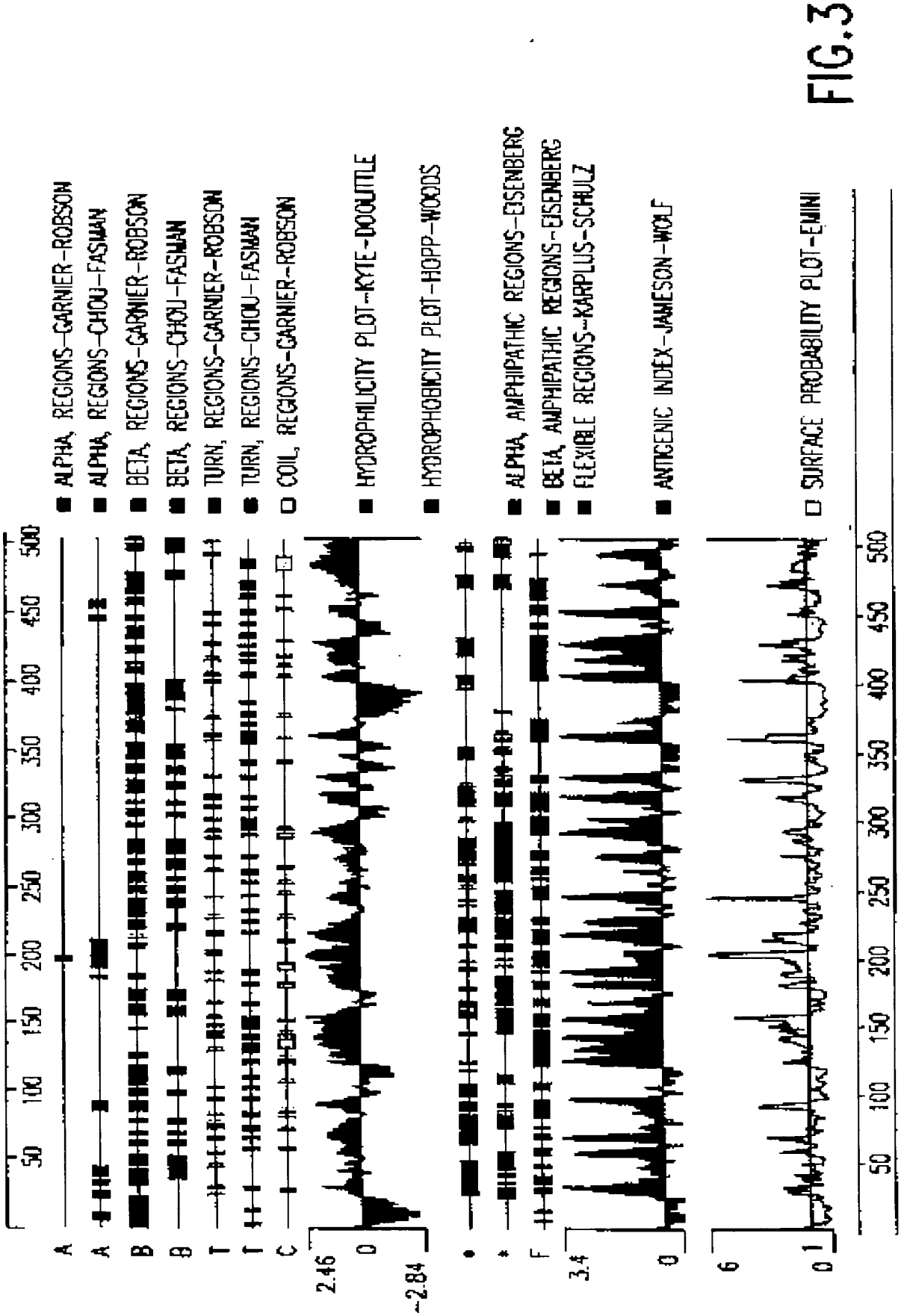

FIG.3

BNSDOCID <WO 0024756A1TI >

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Met	1	.	.	B	.	.	.	.	0.31	.	.	.	0.05	1.11
Thr	2	.	.	B	.	.	T	.	-0.11	.	.	.	0.25	1.34
Pro	3	.	.	B	.	.	T	.	-0.53	.	.	.	-0.20	0.87
Ser	4	.	.	B	.	.	T	.	-0.96	.	.	.	-0.20	0.72
Pro	5	.	.	B	.	.	T	.	-1.38	.	.	F	-0.05	0.41
Leu	6	.	A	B	.	.	.	.	-1.59	.	.	F	-0.45	0.22
Leu	7	.	A	B	.	.	.	.	-2.09	.	.	.	-0.60	0.14
Leu	8	.	A	B	.	.	.	.	-2.09	.	.	.	-0.60	0.07
Leu	9	.	A	B	.	.	.	.	-2.00	.	.	.	-0.60	0.14
Leu	10	.	A	B	.	.	.	.	-2.60	.	.	.	-0.60	0.25
Leu	11	.	A	B	.	.	.	.	-2.60	.	.	.	-0.60	0.25
Pro	12	.	.	B	.	.	T	.	-2.60	.	.	F	-0.05	0.25
Pro	13	.	.	B	.	.	T	.	-2.13	.	.	F	-0.05	0.25
Leu	14	.	.	B	.	.	T	.	-1.91	.	.	.	-0.20	0.30
Leu	15	.	.	B	.	.	T	.	-1.80	.	.	.	-0.20	0.20
Leu	16	.	.	B	.	.	.	.	-1.20	.	.	.	-0.40	0.11
Gly	17	.	.	B	.	.	.	.	-1.20	.	.	.	-0.40	0.21
Ala	18	.	.	B	.	.	.	.	-1.58	.	.	.	-0.40	0.39
Phe	19	.	.	B	.	.	.	.	-1.36	.	.	.	-0.40	0.48
Pro	20	.	.	B	.	.	.	.	-1.13	.	.	.	-0.40	0.49
Pro	21	.	A	B	.	.	.	.	-0.91	.	.	.	-0.60	0.49
Ala	22	.	A	B	.	.	.	.	-0.46	.	*	.	-0.60	0.57
Ala	23	.	A	B	.	.	.	.	-0.21	.	.	.	0.30	0.72
Ala	24	.	A	B	.	.	.	.	0.28	.	*	.	0.30	0.46
Ala	25	.	A	.	.	T	.	.	0.28	*	*	.	0.70	0.71

FIG. 4A

SUBSTITUTE SHEET (RULE 26)

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Arg	26	.	A	.	.	.	.	C	0.53	*	*	F	1.14	1.08
Gly	27	.	A	.	.	.	.	C	0.52	*	*	F	1.78	2.15
Pro	28	.	.	.	.	.	T	C	0.52	*	*	F	2.52	2.10
Pro	29	.	.	.	.	.	T	C	1.11	*	*	F	2.86	1.08
Lys	30	.	.	.	.	T	T	.	1.74	*	*	F	3.40	1.83
Met	31	.	.	B	.	.	T	.	0.78	*	*	.	2.51	2.37
Ala	32	.	A	B	.	.	.	.	0.27	*	.	.	1.77	1.14
Asp	33	.	A	B	.	.	.	.	0.27	*	*	F	1.43	0.42
Lys	34	.	A	B	.	.	.	.	0.59	*	*	F	0.79	0.66
Val	35	.	A	B	.	.	.	.	0.54	*	.	F	0.90	1.28
Val	36	.	.	B	B	.	.	.	0.29	*	.	F	0.90	1.32
Pro	37	.	.	B	B	.	.	.	0.29	*	*	F	0.45	0.49
Arg	38	.	A	B	B	.	.	.	0.40	*	*	F	-0.15	0.67
Gln	39	.	A	B	B	.	.	.	-0.46	*	*	.	0.45	1.77
Val	40	.	A	B	B	.	.	.	0.06	*	.	.	0.30	0.94
Ala	41	.	A	B	B	.	.	.	1.02	*	.	.	0.30	0.48
Arg	42	.	A	B	B	.	.	.	0.92	*	.	.	0.30	0.54
Leu	43	.	A	B	B	.	.	.	-0.04	*	*	.	0.45	1.05
Gly	44	.	A	.	B	T	.	.	0.07	*	*	F	0.85	0.77
Arg	45	.	.	B	B	.	.	.	0.11	*	*	F	0.75	0.77
Thr	46	.	.	B	B	.	.	.	0.70	*	*	F	0.45	0.77
Val	47	.	.	B	B	.	.	.	-0.08	*	*	.	0.45	1.35
Arg	48	.	.	B	B	.	.	.	0.52	*	*	.	0.30	0.37
Leu	49	.	.	B	B	.	.	.	0.01	*	*	.	-0.30	0.39
Gln	50	.	.	B	B	.	.	.	-0.10	*	*	.	0.00	0.39

FIG. 4B

BNSDOCID: <WO 0024756A1 >

SUBSTITUTE SHEET (RULE 26)

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Cys	51			B	B				-0.13		*		0.90	0.35
Pro	52			B	B				0.72		*		0.60	0.42
Val	53					T			0.40		*		2.40	0.40
Glu	54					T			1.00		*	F	3.00	1.16
Gly	55					T			0.79		*	F	2.70	1.16
Asp	56						T	C	0.64			F	2.40	2.43
Pro	57						T	C	0.54			F	2.10	1.16
Pro	58						T	C	0.80			F	1.50	1.68
Pro	59						T	C	0.51			F	0.45	1.00
Leu	60			B	B				0.54				-0.60	0.68
Thr	61			B	B				0.59				-0.26	0.63
Met	62			B	B				0.80	*			0.08	0.82
Trp	63			B	B				0.67	*			0.87	1.66
Thr	64			B			T		0.99	*		F	2.36	1.14
Lys	65					T	T		1.49	*		F	3.40	2.25
Asp	66					T	I		0.91	*		F	3.06	3.09
Gly	67					T	T		1.48	*		F	2.72	1.50
Arg	68			B	B				1.47	*		F	1.58	1.02
Thr	69			B	B				1.43	*		F	1.09	0.82
Ile	70			B	B				1.10	*			0.30	0.82
His	71						I	C	0.80	*			0.30	0.44
Ser	72						I	C	1.26	*			0.00	0.41
Gly	73					T	T		0.44	*	*	F	0.80	1.14
Trp	74					T	I		0.87	*	*	F	0.65	0.73
Ser	75				B			C	0.90	*	*		0.65	1.06

FIG. 4C

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpt_ Flexi_	James_ Antig_	Emini Surfa_
Arg	76	.	.	.	B	T	.	.	0.12	*	*	.	0.10	0.80
Phe	77	.	.	B	B	.	.	.	0.21	*	*	.	-0.60	0.62
Arg	78	.	.	B	B	.	.	.	0.56	*	*	.	0.30	0.72
Val	79	.	.	B	B	.	.	.	0.50	*	*	.	0.30	0.64
Leu	80	.	.	B	B	.	.	.	-0.01	*	*	.	-0.30	0.73
Pro	81	.	.	.	.	.	T	C	-0.08	*	*	F	0.45	0.31
Gln	82	.	.	.	.	T	T	.	-0.23	*	*	F	0.65	0.83
Gly	83	.	.	.	.	.	T	C	-0.30	*	*	F	0.45	0.74
Leu	84	.	.	.	.	.	T	C	0.56	.	.	F	1.05	0.96
Lys	85	.	A	B	.	.	.	.	0.51	.	.	F	0.45	0.96
Val	86	.	A	B	.	.	.	.	0.72	*	*	F	0.45	0.72
Lys	87	.	A	B	.	.	.	.	0.83	*	.	F	0.90	1.51
Gln	88	.	A	B	.	.	.	.	1.18	*	*	F	0.90	1.48
Val	89	.	A	B	.	.	.	.	1.99	*	*	F	0.90	3.46
Glu	90	.	A	B	.	.	.	.	1.36	*	*	F	1.21	2.89
Arg	91	.	A	B	.	.	.	.	1.87	*	.	F	1.52	1.69
Glu	92	.	A	B	.	.	.	.	0.97	*	.	F	1.83	2.25
Asp	93	.	.	.	.	T	T	.	0.72	.	.	F	2.79	0.96
Ala	94	.	.	.	.	T	T	.	0.72	.	.	F	3.10	0.77
Gly	95	.	.	.	.	T	T	.	0.06	.	.	.	2.34	0.33
Val	96	.	.	B	.	.	T	.	-0.01	.	*	.	0.73	0.11
Tyr	97	.	.	B	B	.	.	.	-0.60	*	.	.	0.02	0.21
Val	98	.	.	B	B	.	.	.	-0.91	*	.	.	-0.29	0.21
Cys	99	.	.	B	B	.	.	.	-0.32	.	.	.	-0.60	0.42
Lys	100	.	.	B	B	.	.	.	-0.32	*	.	.	-0.30	0.43

FIG. 4D

BNSDOCID <WO 0024756A1 >

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Ala	101	.	.	B	.	.	T	.	-0.17	*	.	F	0.25	0.57
Thr	102	.	.	B	.	.	T	.	-0.27	*	.	F	0.25	0.92
Asn	103	.	.	.	.	T	T	.	0.29	*	.	F	0.65	0.46
Gly	104	.	.	.	.	T	T	.	0.14	*	.	F	0.35	0.60
Phe	105	.	.	B	.	.	.	.	-0.20	*	.	F	-0.25	0.35
Gly	106	.	.	.	.	.	.	C	-0.47	.	*	F	-0.05	0.29
Ser	107	.	.	B	.	.	.	.	-0.16	.	*	.	-0.40	0.22
Leu	108	.	.	B	.	.	.	.	-0.40	.	*	.	-0.40	0.40
Ser	109	.	.	B	.	.	T	.	-0.37	.	*	.	-0.20	0.63
Val	110	.	.	B	.	.	T	.	-0.48	.	.	.	-0.20	0.68
Asn	111	.	.	B	.	.	T	.	-0.99	.	*	.	-0.20	0.68
Tyr	112	.	.	B	.	.	T	.	-1.54	.	*	.	-0.20	0.38
Thr	113	.	.	B	B	.	.	.	-1.54	.	*	.	-0.60	0.38
Leu	114	.	.	B	B	.	.	.	-1.24	.	.	.	-0.60	0.19
Val	115	.	.	B	B	.	.	.	-0.39	*	.	.	-0.60	0.21
Val	116	.	.	B	B	.	.	.	-1.28	*	.	.	-0.30	0.24
Leu	117	.	.	B	B	.	.	.	-1.33	.	.	.	-0.30	0.20
Asp	118	.	.	B	B	.	.	.	-1.23	.	.	F	-0.15	0.37
Asp	119	.	.	B	.	.	.	.	-0.77	.	.	F	0.99	0.77
Ile	120	.	.	B	.	.	.	.	0.13	*	.	F	1.33	0.92
Ser	121	.	.	.	.	.	T	C	0.99	*	.	F	2.52	1.10
Pro	122	.	.	.	.	.	T	C	1.50	*	.	F	2.86	1.14
Gly	123	.	.	.	.	T	T	.	0.69	*	.	F	3.40	2.18
Lys	124	.	.	.	.	.	T	C	0.34	.	.	F	2.86	1.34
Glu	125	.	.	B	.	.	.	.	1.02	.	.	F	1.97	0.86

FIG. 4E

SUBSTITUTE SHEET (RULE 26)

BNSDOCID <WO 0024756A1T1 >

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jomes_ Antig_	Emini Surfa_
Ser	126	.	.	B	.	.	.	.	1.32	.	.	F	1.78	1.34
Leu	127	.	.	B	.	.	.	.	1.23	.	.	F	1.74	1.12
Gly	128	.	.	B	.	.	T	.	1.28	.	.	F	1.75	0.87
Pro	129	.	.	.	.	.	T	C	0.93	.	.	F	1.95	0.87
Asp	130	.	.	.	.	T	T	.	0.59	.	.	F	2.60	1.41
Ser	131	.	.	.	.	.	T	C	0.54	.	.	F	3.00	1.41
Ser	132	.	.	.	.	.	T	C	1.36	.	.	F	2.55	0.90
Ser	133	.	.	.	.	.	T	C	1.70	.	.	F	2.25	0.94
Gly	134	.	.	.	.	.	T	C	1.91	.	.	F	2.10	1.21
Gly	135	.	.	.	.	.	T	C	1.70	.	.	F	1.80	1.51
Gln	136	.	.	.	.	.	.	C	1.41	.	.	F	1.64	1.74
Glu	137	.	.	.	.	.	.	C	1.41	.	.	F	1.98	1.77
Asp	138	.	.	.	.	.	T	C	1.71	.	.	F	2.52	2.40
Pro	139	.	.	.	.	.	T	C	2.06	.	.	F	2.86	2.40
Ala	140	.	.	.	.	T	T	.	2.11	.	.	F	3.40	2.40
Ser	141	.	.	.	.	.	T	C	1.52	*	.	F	1.96	1.51
Gln	142	.	.	B	.	.	.	.	1.63	*	.	F	0.77	0.99
Gln	143	.	.	.	.	T	.	.	1.42	*	*	F	1.28	1.92
Trp	144	.	.	.	.	T	.	.	1.74	.	*	F	0.94	2.21
Ala	145	.	.	B	.	.	.	.	1.63	.	*	.	0.65	2.50
Arg	146	.	.	B	.	.	T	.	1.62	.	*	.	0.25	1.25
Pro	147	.	.	B	.	.	T	.	1.62	.	*	F	0.40	1.72
Arg	148	.	.	.	.	T	T	.	1.41	.	*	F	1.40	2.94
Phe	149	.	.	.	.	T	T	.	1.40	.	*	F	1.74	2.32
Thr	150	.	.	.	.	.	.	C	2.03	.	*	F	1.68	2.01

FIG. 4F

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jomes_ Antig_	Emini Surfa_
Gln	151	.	.	.	.	.	T	C	1.32	.	*	F	2.52	2.06
Pro	152	.	.	.	.	.	T	C	1.64	.	*	F	1.96	2.35
Ser	153	.	.	.	.	T	T	.	1.64	*	*	F	3.40	3.19
Lys	154	.	.	.	.	T	T	.	2.46	*	*	F	3.06	3.61
Met	155	.	.	B	.	.	.	.	1.91	*	*	F	2.12	4.57
Arg	156	.	.	B	B	.	.	.	1.02	*	*	F	1.58	2.53
Arg	157	.	.	B	B	.	.	.	0.64	*	*	F	1.09	0.89
Arg	158	.	.	B	B	.	.	.	1.06	*	*	.	0.60	0.91
Val	159	.	.	B	B	.	.	.	0.80	*	*	.	0.60	0.91
Ile	160	.	.	B	B	.	.	.	0.54	.	*	.	0.60	0.71
Ala	161	.	.	B	B	.	.	.	0.09	*	*	.	0.55	0.27
Arg	162	.	.	B	B	.	.	.	-0.32	*	.	.	0.20	0.36
Pro	163	.	.	B	.	.	T	.	-0.73	*	*	F	1.00	0.69
Val	164	.	.	.	.	T	T	.	-0.73	*	*	F	2.25	0.92
Gly	165	.	.	.	.	T	T	.	0.27	*	*	F	2.50	0.35
Ser	166	.	.	B	.	.	T	.	0.04	*	*	F	1.85	0.44
Ser	167	.	.	B	B	.	.	.	-0.02	*	*	F	0.60	0.49
Val	168	.	.	B	B	.	.	.	-0.48	.	*	F	0.95	0.99
Arg	169	.	.	B	B	.	.	.	-0.48	.	*	.	0.55	0.39
Leu	170	.	.	B	B	.	.	.	-0.72	.	*	.	0.30	0.22
Lys	171	.	.	B	B	.	.	.	-0.72	.	*	.	-0.30	0.30
Cys	172	.	.	B	B	.	.	.	-0.77	.	*	.	0.30	0.20
Val	173	.	.	B	B	.	.	.	0.06	.	*	.	-0.30	0.24
Ala	174	.	.	B	B	.	.	.	-0.27	*	*	.	0.00	0.17
Ser	175	.	.	B	B	.	.	.	0.66	*	*	.	0.00	0.48

FIG. 4G

SUBSTITUTE SHEET (RULE 26)

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Gly	176	.	.	.	.	.	.	C	0.40	*	*	F	1.90	1.27
His	177	.	.	.	.	.	T	C	1.07	.	*	F	2.40	1.94
Pro	178	.	.	.	.	.	T	C	1.03	.	*	F	3.00	2.41
Arg	179	.	.	.	.	.	T	C	1.31	.	*	F	2.70	1.71
Pro	180	.	.	.	.	T	T	.	1.32	.	*	F	2.30	1.81
Asp	181	.	.	.	.	T	.	.	1.07	.	*	F	1.80	1.23
Ile	182	.	A	B	.	.	.	.	1.14	*	*	.	0.00	0.62
Thr	183	.	A	B	.	.	.	.	1.36	*	*	.	0.04	0.81
Trp	184	.	A	B	.	.	.	.	1.24	.	*	.	0.98	0.81
Met	185	.	A	B	.	.	.	.	1.46	.	.	.	1.47	1.92
Lys	186	.	.	B	.	.	T	.	0.87	.	.	.	2.51	2.30
Asp	187	.	.	.	.	T	T	.	0.94	.	.	F	3.40	2.21
Asp	188	.	.	.	.	T	T	.	0.94	*	.	F	3.06	1.84
Gln	189	.	.	.	.	.	T	C	1.34	*	.	F	2.52	1.33
Ala	190	.	A	.	.	.	.	C	1.73	*	.	.	1.63	1.56
Leu	191	.	A	.	.	.	.	C	1.69	*	*	F	1.14	1.45
Thr	192	.	A	.	.	.	.	C	1.10	.	*	F	0.80	1.45
Arg	193	.	A	.	.	.	.	C	0.51	.	.	F	0.80	1.45
Pro	194	.	A	.	.	.	.	C	0.51	.	.	F	0.80	1.77
Glu	195	A	A	.	.	.	.	.	0.89	*	.	F	0.90	2.13
Ala	196	A	A	.	.	.	.	.	1.81	*	.	F	0.90	1.68
Ala	197	A	A	.	.	.	.	.	2.17	.	*	F	0.90	2.13
Glu	198	A	A	.	.	.	.	.	2.10	.	.	F	0.90	2.45
Pro	199	A	A	.	.	.	.	.	2.36	.	.	F	0.90	4.86
Arg	200	.	A	.	.	T	.	.	2.07	.	.	F	1.30	9.62

FIG. 4H

SUBSTITUTE SHEET (RULE 26)

BNSDOCID <WO 0024756A1 >

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Lys	201	A	A	.	.	.	.	.	2.34	.	.	F	0.90	5.84
Lys	202	.	A	.	.	I	.	.	2.12	.	.	F	1.30	5.45
Lys	203	.	A	.	.	I	.	.	1.82	.	*	F	1.30	2.29
Trp	204	.	A	B	.	.	.	.	1.22	.	*	.	0.75	1.54
Thr	205	.	A	B	.	.	.	.	1.16	.	*	.	-0.30	0.63
Leu	206	.	A	B	.	.	.	.	1.11	*	*	.	-0.30	0.63
Ser	207	.	A	B	.	.	.	.	0.26	*	.	.	-0.60	0.97
Leu	208	.	A	B	.	.	.	.	0.32	*	*	.	-0.30	0.55
Lys	209	.	A	.	.	T	.	.	0.40	*	*	F	1.00	1.32
Asn	210	.	A	.	.	.	.	C	0.71	.	.	F	0.80	1.52
Leu	211	.	A	.	.	.	.	C	1.52	.	.	F	1.44	3.19
Arg	212	.	A	B	.	.	.	.	1.52	.	.	F	1.58	2.66
Pro	213	.	.	B	.	.	.	.	1.99	.	*	F	2.12	2.22
Glu	214	.	.	.	.	T	.	.	1.99	.	*	F	2.86	2.66
Asp	215	.	.	.	.	T	T	.	1.74	.	*	F	3.40	2.72
Ser	216	.	.	.	.	T	T	.	2.24	.	*	F	3.06	2.76
Gly	217	.	.	.	.	T	T	.	1.47	*	*	F	2.72	2.30
Lys	218	.	.	.	.	T	T	.	1.79	*	*	F	1.93	0.74
Tyr	219	.	.	B	B	.	.	.	0.93	*	*	F	0.94	1.08
Thr	220	.	.	B	B	.	.	.	0.63	*	*	.	0.56	0.81
Cys	221	.	.	B	B	.	.	.	0.93	*	*	.	0.82	0.54
Arg	222	.	.	B	B	.	.	.	1.39	*	*	.	0.48	0.56
Val	223	.	.	B	.	.	T	.	0.76	*	*	.	2.04	0.75
Ser	224	.	.	B	.	.	T	.	0.66	*	*	F	2.60	1.42
Asn	225	.	.	B	.	.	T	.	0.38	*	*	F	2.19	0.72
Arg	226	.	.	.	.	T	T	.	0.16	*	*	F	2.03	0.98

FIG. 4I

BNSDOCID <WO 0024756A1T1 >

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jomes_ Antig_	Emini Surfa_
Ala	227	.	.	.	.	T	.	C	0.04	*	*	F	1.57	0.51
Gly	228	.	.	.	.	.	.	C	0.31	.	.	.	0.96	0.51
Ala	229	.	.	B	.	.	.	.	0.30	.	.	.	-0.10	0.26
Ile	230	.	.	B	.	.	.	.	0.06	.	*	.	-0.40	0.38
Asn	231	.	.	B	.	.	I	.	-0.01	.	*	.	-0.20	0.60
Ala	232	.	.	B	.	.	I	.	-0.28	.	*	.	0.25	1.18
Thr	233	.	.	B	.	.	I	.	0.07	.	*	.	-0.05	1.25
Tyr	234	.	.	B	.	.	I	.	-0.20	.	*	.	0.85	1.30
Lys	235	.	.	B	B	.	.	.	-0.20	.	*	.	-0.30	0.95
Val	236	.	.	B	B	.	.	.	-0.20	*	*	.	-0.30	0.46
Asp	237	.	.	B	B	.	.	.	0.50	*	*	.	-0.30	0.51
Val	238	.	.	B	B	.	.	.	0.50	.	*	.	0.60	0.50
Ile	239	.	.	B	B	.	.	.	0.86	.	*	.	0.64	0.98
Gln	240	.	.	B	B	.	.	.	0.51	*	*	.	1.43	1.14
Arg	241	.	.	B	B	.	.	.	1.41	*	*	F	1.62	2.06
Thr	242	.	.	.	.	I	I	.	1.20	*	*	F	3.06	5.89
Arg	243	.	.	.	.	T	T	.	1.20	.	*	F	3.40	5.26
Ser	244	.	.	.	.	.	I	C	1.28	.	*	F	2.86	1.99
Lys	245	.	.	.	.	.	T	C	0.97	.	*	F	2.22	1.14
Pro	246	.	.	B	B	.	.	.	0.51	.	*	F	1.13	0.84
Val	247	.	.	B	B	.	.	.	0.51	.	*	F	0.19	0.62
Leu	248	.	.	B	B	.	.	.	0.37	.	*	F	-0.15	0.45
Thr	249	.	.	B	B	.	.	.	0.46	*	.	F	-0.45	0.39
Gly	250	.	.	B	B	.	.	.	-0.44	*	.	F	-0.45	0.82
Thr	251	.	.	B	B	.	.	.	-0.23	.	.	F	-0.45	0.74

FIG. 4J

SUBSTITUTE SHEET (RULE 26)

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jomes_ Antig_	Emini Surfa_
His	252	.	.	.	.	.	T	C	0.31	.	.	F	0.45	0.82
Pro	253	.	.	.	.	.	T	C	0.81	.	.	.	0.45	1.20
Val	254	.	.	B	.	.	T	.	0.27	*	*	.	-0.05	1.20
Asn	255	.	.	B	.	.	T	.	0.61	*	*	F	-0.05	0.65
Thr	256	.	.	B	B	.	.	.	0.22	*	*	F	-0.15	0.71
Thr	257	.	.	B	B	.	.	.	-0.09	*	*	F	-0.45	0.82
Val	258	.	.	B	B	.	.	.	-0.22	*	*	.	-0.30	0.51
Asp	259	.	.	B	.	.	I	.	0.32	*	*	.	0.10	0.35
Phe	260	.	.	B	.	.	T	.	0.01	.	*	F	0.25	0.35
Gly	261	.	.	.	.	T	T	.	0.02	.	*	F	0.65	0.68
Gly	262	.	.	.	.	T	T	.	-0.37	.	*	F	1.25	0.54
Thr	263	.	.	.	B	.	.	C	0.49	.	*	F	-0.25	0.54
Thr	264	.	.	.	B	.	.	C	-0.18	.	*	F	0.05	0.95
Ser	265	.	.	.	B	.	.	C	0.57	.	*	F	-0.25	0.51
Phe	266	.	.	B	B	.	.	.	0.06	*	*	.	-0.15	0.71
Gln	267	.	.	B	B	.	.	.	0.51	*	*	.	0.00	0.37
Cys	268	.	.	B	B	.	.	.	0.52	.	*	.	0.75	0.54
Lys	269	.	.	B	B	.	.	.	0.83	*	*	.	0.90	0.83
Val	270	.	.	B	B	.	.	.	0.28	*	*	F	1.50	0.80
Arg	271	.	.	B	.	.	T	.	1.02	*	*	F	1.90	1.11
Ser	272	.	.	.	.	T	T	.	0.81	*	*	F	2.15	1.11
Asp	273	.	.	.	.	T	T	.	0.62	*	*	F	2.00	2.31
Val	274	.	.	B	.	.	T	.	-0.31	*	*	F	1.30	0.87
Lys	275	.	.	B	B	.	.	.	0.54	*	*	F	0.45	0.46
Pro	276	.	.	B	B	.	.	.	0.14	*	*	F	0.45	0.47

FIG. 4K

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jones_ Antig_	Emini Surfa_
Val	277	.	.	B	B	.	.	.	-0.37	*	*	.	-0.60	0.67
Ile	278	.	.	B	B	.	.	.	-0.32	*	*	.	-0.60	0.28
Gln	279	.	.	B	B	.	.	.	0.64	*	*	.	-0.60	0.36
Trp	280	.	.	B	B	.	.	.	-0.26	*	*	.	-0.30	0.95
Leu	281	.	.	B	B	.	.	.	-0.04	*	*	.	-0.15	1.00
Lys	282	.	.	B	B	.	.	.	0.57	*	*	.	0.45	1.00
Arg	283	.	.	B	B	.	.	.	1.11	*	*	.	0.45	1.49
Val	284	.	.	B	B	.	.	.	0.52	*	*	.	0.45	1.79
Glu	285	.	.	B	B	.	.	.	0.81	*	*	.	0.60	0.90
Tyr	286	.	.	.	.	I	.	C	1.28	*	*	.	1.54	0.80
Gly	287	.	.	.	.	.	T	C	1.34	.	*	.	1.73	1.07
Ala	288	.	.	.	.	.	T	C	1.20	.	*	F	2.52	1.21
Glu	289	.	.	.	.	.	T	C	2.06	.	*	F	2.56	1.05
Gly	290	.	.	.	.	T	T	.	1.76	.	*	F	3.40	1.70
Arg	291	.	.	.	.	T	.	.	1.69	.	*	F	2.86	2.26
His	292	.	.	.	.	.	T	C	1.14	.	*	F	2.52	1.88
Asn	293	.	.	.	.	.	T	C	1.73	.	*	F	1.88	1.33
Ser	294	.	.	S	.	.	T	.	0.88	.	*	F	1.64	1.14
Thr	295	.	.	B	.	.	T	.	0.88	.	*	F	0.25	0.62
Ile	296	.	.	B	.	.	.	.	0.42	*	*	F	0.30	0.38
Asp	297	.	.	B	.	.	T	.	0.46	.	*	F	0.75	0.28
Val	298	.	.	B	.	.	T	.	0.50	*	*	F	1.00	0.34
Gly	299	.	.	.	.	I	I	.	0.10	*	.	F	2.25	0.96
Gly	300	.	.	.	.	I	I	.	-0.44	.	.	F	2.50	0.50
Gln	301	.	.	B	B	.	.	.	-0.41	*	.	F	0.85	0.50

FIG. 4L

BNSDOCID <WO 0024756A1 >

SUBSTITUTE SHEET (RULE 26)

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Lys	302	.	.	B	B	.	.	.	-1.22	.	.	F	0.60	0.37
Phe	303	.	.	B	B	.	.	.	-0.58	.	.	.	-0.10	0.31
Val	304	.	.	B	B	.	.	.	-0.54	.	.	.	-0.35	0.28
Val	305	.	.	B	B	.	.	.	-0.54	.	.	.	-0.60	0.20
Leu	306	.	.	B	.	.	T	.	-0.54	.	.	.	-0.20	0.23
Pro	307	.	.	B	.	.	T	.	-1.44	.	.	F	0.25	0.52
Thr	308	.	.	.	.	T	T	.	-1.03	.	.	F	0.65	0.52
Gly	309	.	.	.	.	T	T	.	-0.48	*	*	F	0.35	0.66
Asp	310	.	.	.	B	T	.	.	0.49	*	*	F	0.25	0.57
Val	311	.	.	B	B	.	.	.	1.09	.	*	F	0.45	0.78
Trp	312	.	.	B	B	.	.	.	1.30	*	*	F	0.94	1.21
Ser	313	.	.	B	B	.	.	.	1.27	*	*	F	1.58	1.21
Arg	314	.	.	B	.	.	T	.	1.31	*	*	F	2.02	1.62
Pro	315	.	.	.	.	T	T	.	1.07	*	*	F	2.76	2.06
Asp	316	.	.	.	.	T	T	.	1.11	*	*	F	3.40	2.41
Gly	317	.	.	.	.	T	T	.	1.40	*	.	F	2.76	1.01
Ser	318	.	.	.	.	T	.	.	1.74	*	*	F	1.62	1.06
Tyr	319	.	.	B	.	.	.	.	0.82	*	*	F	1.48	1.26
Leu	320	.	.	B	.	.	.	.	0.22	.	.	F	0.54	1.05
Asn	321	.	.	B	.	.	.	.	-0.67	*	.	.	-0.40	0.65
Lys	322	.	.	B	B	.	.	.	-0.63	.	.	.	-0.60	0.29
Leu	323	.	.	B	B	.	.	.	-0.22	.	.	.	-0.60	0.51
Leu	324	.	.	B	B	.	.	.	-0.57	*	*	.	0.30	0.62
Ile	325	.	.	B	B	.	.	.	0.36	*	*	.	-0.30	0.31
Thr	326	.	.	B	B	.	.	.	0.36	.	*	.	0.04	0.74

FIG. 4M

SUBSTITUTE SHEET (RULE 26)

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Arg	327	.	.	B	B	.	.	.	0.31	.	*	F	1.28	1.56
Ala	328	.	.	B	B	.	.	.	1.12	.	*	F	1.92	3.71
Arg	329	.	.	B	.	.	T	.	1.34	.	*	F	2.66	4.29
Gln	330	.	.	.	.	T	T	.	1.89	.	.	F	3.40	2.21
Asp	331	.	.	.	.	T	T	.	1.60	.	*	F	3.06	2.17
Asp	332	.	.	.	.	T	T	.	1.24	.	*	F	2.72	1.10
Ala	333	.	.	.	.	T	.	.	0.94	.	.	.	1.58	0.99
Gly	334	.	.	B	B	.	.	.	0.17	.	.	.	0.64	0.42
Met	335	.	.	B	B	.	.	.	-0.64	.	.	.	-0.60	0.13
Tyr	336	.	.	B	B	.	.	.	-0.99	.	.	.	-0.60	0.11
Ile	337	.	.	B	B	.	.	.	-1.58	.	*	.	-0.60	0.11
Cys	338	.	.	B	B	.	.	.	-0.99	.	.	.	-0.60	0.11
Leu	339	.	.	B	B	.	.	.	-0.96	.	.	.	-0.60	0.11
Gly	340	.	.	B	.	.	T	.	-0.96	.	.	.	-0.20	0.24
Ala	341	.	.	B	.	.	T	.	-1.06	.	.	.	-0.20	0.43
Asn	342	.	.	.	.	.	T	C	-0.41	.	.	.	0.00	0.52
Thr	343	.	.	.	.	.	T	C	-0.04	.	.	.	0.00	0.82
Met	344	.	.	B	B	.	.	.	0.07	*	*	.	-0.45	1.09
Gly	345	.	.	B	B	.	.	.	0.52	*	*	.	-0.60	0.59
Tyr	346	.	.	B	B	.	.	.	0.81	*	.	.	-0.60	0.80
Ser	347	.	.	B	B	.	.	.	0.22	*	*	.	-0.15	1.08
Phe	348	.	.	B	B	.	.	.	-0.17	*	*	.	-0.15	1.11
Arg	349	.	.	B	B	.	.	.	-0.38	*	*	.	-0.60	0.61
Ser	350	.	.	B	B	.	.	.	-0.34	*	.	.	-0.60	0.38
Ala	351	.	.	B	B	.	.	.	-0.96	*	*	.	-0.60	0.63

FIG. 4N

BNSDOCID <WO 0024756A1T1 >

SUBSTITUTE SHEET (RULE 26)

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Phe	352	.	.	B	B	.	.	.	-1.47	*	.	.	-0.60	0.24
Leu	353	.	.	B	B	.	.	.	-0.98	*	.	.	-0.60	0.15
Thr	354	.	.	B	B	.	.	.	-1.09	.	.	.	-0.60	0.22
Val	355	.	.	B	B	.	.	.	-1.00	.	.	.	-0.60	0.43
Leu	356	.	.	B	.	.	T	.	-0.37	.	.	.	0.10	0.81
Pro	357	.	.	.	.	T	T	.	0.12	.	*	F	1.74	1.12
Asp	358	.	.	.	.	T	T	.	0.93	.	*	F	2.08	2.33
Pro	359	.	.	.	.	.	T	C	0.90	.	*	F	2.52	4.90
Lys	360	.	.	.	.	.	.	C	1.54	.	*	F	2.66	3.14
Pro	361	.	.	.	.	T	T	.	2.14	.	.	F	3.40	2.90
Gln	362	.	.	.	.	T	T	.	1.50	.	*	F	2.76	2.90
Gly	363	.	.	B	.	.	T	.	0.91	.	*	F	2.02	1.08
Pro	364	.	.	B	.	.	T	.	0.82	.	.	F	0.93	0.70
Pro	365	.	.	B	.	.	.	.	0.48	.	.	F	0.39	0.55
Val	366	.	.	B	.	.	.	.	0.39	.	.	F	0.05	0.74
Ala	367	.	.	B	.	.	.	.	0.09	.	.	F	0.05	0.64
Ser	368	.	.	B	.	.	T	.	-0.16	.	.	F	0.25	0.55
Ser	369	.	.	B	.	.	T	.	-0.26	.	.	F	0.34	0.75
Ser	370	.	.	B	.	.	T	.	-0.34	.	.	F	0.58	1.08
Ser	371	.	.	.	.	.	T	C	-0.30	.	.	F	1.47	1.08
Ala	372	.	.	B	.	.	.	.	0.08	.	.	F	0.41	0.66
Thr	373	.	.	.	.	T	.	.	0.09	.	.	F	0.90	0.77
Ser	374	.	.	.	.	.	.	C	0.18	.	.	F	0.31	0.60
Leu	375	.	.	.	.	.	T	C	-0.38	.	.	.	0.27	0.92
Pro	376	.	.	B	.	.	T	.	-0.93	.	.	.	-0.02	0.47

FIG. 40

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Trp	377	.	.	B	.	.	T	.	-1.23	.	.	.	-0.11	0.26
Pro	378	.	.	B	.	.	T	.	-1.27	.	*	.	-0.20	0.22
Val	379	.	.	B	B	.	.	.	-1.86	.	*	.	-0.60	0.14
Val	380	.	.	B	B	.	.	.	-1.26	.	*	.	-0.60	0.09
Ile	381	.	.	B	B	.	.	.	-1.63	.	.	.	-0.60	0.09
Gly	382	.	.	B	.	.	.	.	-1.69	.	.	.	-0.40	0.13
Ile	383	.	.	B	.	.	.	.	-2.07	.	.	.	-0.40	0.17
Pro	384	.	.	B	.	.	T	.	-2.07	.	.	.	-0.20	0.25
Ala	385	.	.	B	.	.	T	.	-1.91	.	.	.	-0.20	0.19
Gly	386	.	.	B	.	.	T	.	-1.91	.	.	.	-0.20	0.23
Ala	387	.	.	B	.	.	T	.	-2.38	.	.	.	-0.20	0.10
Val	388	.	.	B	B	.	.	.	-1.83	.	.	.	-0.60	0.09
Phe	389	.	.	B	B	.	.	.	-1.93	.	.	.	-0.60	0.09
Ile	390	.	.	B	B	.	.	.	-2.16	.	.	.	-0.60	0.12
Leu	391	.	.	B	B	.	.	.	-2.62	.	.	.	-0.60	0.14
Gly	392	.	.	B	B	.	.	.	-2.84	.	.	.	-0.60	0.13
Thr	393	.	.	B	B	.	.	.	-2.28	.	.	.	-0.60	0.15
Leu	394	.	.	B	B	.	.	.	-2.39	.	.	.	-0.60	0.19
Leu	395	.	.	B	B	.	.	.	-2.17	*	.	.	-0.60	0.16
Leu	396	.	.	B	B	.	.	.	-1.36	*	.	.	-0.60	0.06
Trp	397	.	.	B	B	.	.	.	-1.60	.	.	.	-0.60	0.13
Leu	398	.	.	B	B	.	.	.	-1.29	*	.	.	-0.60	0.15
Cys	399	.	.	B	B	.	.	.	-0.43	*	.	.	-0.60	0.32
Gln	400	.	.	.	B	T	.	.	0.42	*	.	.	-0.20	0.61
Ala	401	.	.	.	B	T	.	.	1.02	.	.	.	1.19	1.49

FIG. 4P

SUBSTITUTE SHEET (RULE 26)

BNSDOCID <WO 0024756A1T1 >

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jones_ Antig_	Emini Surfa_
Gln	402	.	.	.	B	T	.	.	0.64	*	.	F	1.98	4.30
Lys	403	.	.	.	.	T	.	.	1.14	*	.	F	2.52	1.33
Lys	404	.	.	.	.	.	T	C	1.60	*	.	F	2.86	1.90
Pro	405	.	.	.	.	T	T	.	1.01	*	.	F	3.40	1.70
Cys	406	.	.	.	.	T	T	.	1.39	.	.	F	2.91	0.86
Thr	407	.	.	B	.	.	T	.	0.80	.	.	F	1.87	0.66
Pro	408	.	.	B	.	.	.	.	0.54	.	.	F	0.73	0.43
Ala	409	.	.	B	.	.	.	.	0.29	.	.	F	0.54	1.25
Pro	410	.	.	B	.	.	.	.	-0.31	.	.	F	0.20	1.34
Ala	411	.	.	.	.	.	.	C	0.14	.	.	F	0.25	0.71
Pro	412	.	.	B	.	.	.	.	0.11	.	.	F	0.48	1.09
Pro	413	.	.	B	.	.	.	.	0.29	.	.	F	0.61	0.70
Leu	414	.	.	B	.	.	T	.	0.99	.	.	F	1.09	0.94
Pro	415	.	.	B	.	.	T	.	0.99	.	.	F	2.12	1.19
Gly	416	.	.	.	.	T	T	.	1.37	.	.	F	2.80	1.19
His	417	.	.	.	.	.	T	C	1.23	.	.	F	2.32	2.24
Arg	418	.	.	.	.	.	.	C	1.13	.	.	F	1.84	1.43
Pro	419	.	.	.	.	.	T	C	1.36	*	.	F	1.76	2.09
Pro	420	.	.	.	.	T	T	.	0.76	*	.	F	1.68	1.55
Gly	421	.	.	B	.	.	T	.	1.10	*	.	F	0.85	0.65
Thr	422	.	.	B	.	.	T	.	1.24	*	.	F	0.85	0.70
Ala	423	.	.	B	.	.	.	.	0.83	*	.	F	0.99	0.89
Leu	424	.	.	B	.	.	.	.	0.70	*	.	F	1.78	1.21
Asp	425	.	.	B	.	.	T	.	0.91	*	.	F	2.17	0.83
Arg	426	.	.	B	.	.	T	.	1.30	*	.	F	2.66	1.37
Ser	427	.	.	.	.	T	T	.	1.61	*	.	F	3.40	3.32

FIG. 4Q

BNSDOCID <WO 0024756A1 >

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jones_ Antig_	Emini Surfa_
Gly	428	.	.	.	.	T	T	.	1.39	*	.	F	3.06	3.32
Asp	429	.	.	.	.	T	.	.	1.99	*	.	F	2.69	1.40
Lys	430	.	.	.	.	T	.	.	1.69	*	.	F	2.52	1.61
Asp	431	.	.	.	.	.	.	C	0.77	*	.	F	2.15	2.18
Leu	432	.	.	B	.	.	T	.	0.48	*	.	F	1.98	1.08
Pro	433	.	.	B	.	.	T	.	0.23	*	.	F	1.70	0.55
Ser	434	.	.	B	.	.	T	.	-0.58	.	.	F	0.93	0.33
Leu	435	.	.	B	.	.	T	.	-0.92	.	.	.	0.31	0.33
Ala	436	.	.	B	.	.	.	.	-1.51	.	.	.	-0.06	0.29
Ala	437	.	.	B	.	.	.	.	-1.04	.	.	.	-0.23	0.22
Leu	438	.	.	B	.	.	.	.	-1.04	.	.	.	-0.40	0.26
Ser	439	.	.	B	.	.	.	.	-1.09	.	.	.	-0.40	0.40
Ala	440	.	.	B	.	.	.	.	-1.13	.	.	F	0.05	0.39
Gly	441	.	.	.	.	.	T	C	-0.89	.	.	F	0.15	0.35
Pro	442	.	.	.	.	T	T	.	-1.11	.	.	F	0.65	0.26
Gly	443	.	.	.	.	T	T	.	-0.97	.	.	F	0.35	0.21
Val	444	.	.	.	.	.	T	C	-0.67	.	.	.	0.00	0.11
Gly	445	.	A	B	.	.	.	.	-0.08	.	.	.	-0.30	0.13
Leu	446	.	A	B	.	.	.	.	0.23	.	.	.	0.30	0.22
Cys	447	.	A	B	.	.	.	.	0.10	.	.	.	0.64	0.41
Glu	448	.	A	B	.	.	.	.	0.14	.	.	.	0.98	0.41
Glu	449	.	A	.	.	T	.	.	0.79	.	.	F	1.87	0.67
His	450	.	.	.	.	T	T	.	0.54	.	.	F	3.06	1.92
Gly	451	.	.	.	.	T	T	.	0.77	.	.	F	3.40	1.12
Ser	452	.	.	.	.	.	T	C	1.22	.	.	F	2.41	0.65
Pro	453	.	.	.	.	.	T	C	1.22	.	.	F	1.47	0.74

FIG. 4R

Res	Pos	Garni_ Alpha	Chou-_ Alpha	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	James_ Antig_	Emini Surfa_
Ala	454	.	A	.	.	-	.	C	1.19	.	.	F	0.88	1.30
Ala	455	.	A	B	.	.	.	.	0.41	.	.	F	0.34	1.32
Pro	456	.	A	B	.	.	.	.	-0.06	.	.	F	-0.45	0.70
Gln	457	.	A	B	.	.	.	.	-0.10	.	.	.	-0.60	0.57
His	458	.	A	B	.	.	.	.	-0.10	.	.	.	-0.60	0.56
Leu	459	.	A	B	.	.	.	.	0.14	.	.	.	-0.60	0.56
Leu	460	.	A	B	.	.	.	.	0.52	.	.	.	-0.60	0.32
Gly	461	.	.	B	.	.	T	.	-0.12	.	.	F	-0.05	0.37
Pro	462	.	.	.	.	.	T	C	-0.71	.	.	F	0.15	0.33
Gly	463	.	.	.	.	.	T	C	-1.02	.	.	F	0.15	0.40
Pro	464	.	.	B	.	.	T	.	-0.42	.	.	F	0.25	0.40
Val	465	.	.	B	.	.	.	.	0.43	.	.	F	0.05	0.40
Ala	466	.	.	B	.	.	.	.	-0.03	.	.	F	0.65	0.81
Gly	467	.	.	B	.	.	T	.	-0.07	.	.	F	0.45	0.43
Pro	468	.	.	B	.	.	T	.	0.07	.	*	F	0.35	0.92
Lys	469	.	.	B	.	.	T	.	0.32	*	*	F	1.00	1.40
Leu	470	.	.	B	.	.	T	.	0.37	*	*	F	1.80	2.83
Tyr	471	.	.	B	.	.	T	.	0.71	*	*	F	2.00	1.51
Pro	472	.	.	B	.	.	T	.	0.74	*	*	F	1.20	1.18
Lys	473	.	.	B	.	.	T	.	0.96	*	*	F	0.70	2.07
Leu	474	.	.	B	.	.	T	.	0.02	*	*	F	0.80	2.21
Tyr	475	.	.	B	B	.	.	.	0.80	*	*	F	0.20	1.00
Thr	476	.	.	B	B	.	.	.	0.73	*	*	F	-0.15	0.68
Asp	477	.	.	B	B	.	.	.	0.91	*	*	.	-0.45	1.19
Ile	478	.	.	B	B	.	.	.	0.56	*	*	.	-0.45	1.03
His	479	.	.	B	B	.	.	.	1.33	.	*	.	-0.15	1.03

FIG. 4S

Res	Pos	Garni_ Alpho	Chou-_ Alpho	Garni_ Beta	Chou-_ Beta	Garni_ Turn	Chou-_ Turn	Garni_ Coil	Kyte-_ Hydro_	Eisen_ Alpha	Eisen_ Beta	Karpl_ Flexi_	Jomes_ Antig_	Emini Surfa_
Thr	480	.	.	B	B	.	.	.	1.27	.	.	.	-0.30	0.84
His	481	.	.	.	B	.	.	C	1.54	.	.	.	-0.25	1.74
Thr	482	.	.	.	B	.	.	C	1.24	.	*	.	-0.25	1.74
His	483	.	.	.	.	.	T	C	2.10	.	.		0.45	1.61
Thr	484	.	.	.	.	.	T	C	1.82	.	.	.	0.45	1.61
His	485	.	.	.	.	.	T	C	2.10	.	.	.	0.45	1.61
Ser	486	.	.	.	.	.	T	C	1.83	.	.	.	0.45	1.61
His	487	.	.	.	.	.	T	C	2.11	.	.	.	0.45	1.50
Thr	488	.	.	.	.	.	T	C	1.29	.	.	.	0.45	1.50
His	489	.	.	.	.	.	T	C	1.60	.	.	.	0.51	0.83
Ser	490	.	.	.	.	.	T	C	1.29	.	*	.	0.87	1.06
His	491	.	.	.	.	.	.	C	1.63	.	*	.	1.33	0.72
Val	492	.	.	.	.	.	.	C	0.81	.	*	.	1.99	1.06
Glu	493	.	.	.	.	T	.	.	1.09	.	*	F	2.10	0.59
Gly	494	.	.	.	B	T	.	.	1.12	.	*	F	1.69	0.59
Lys	495	.	.	.	B	T	.	.	1.39	*	*	F	1.63	1.37
Val	496	.	.	B	B	.	.	.	0.53	*	*	.	1.17	1.08
His	497	.	.	B	B	.	.	.	1.36	*	*	.	-0.09	0.76
Gln	498	.	.	B	B	.	.	.	1.11	.	*	.	-0.30	0.52
His	499	.	.	B	B	.	.	.	1.46	*	*	.	-0.45	1.10
Ile	500	.	.	B	B	.	.	.	0.74	*	*	.	-0.45	1.40
His	501	.	.	B	B	.	.	.	1.21	.	*	.	-0.60	0.43
Tyr	502	.	.	.	B	T	.	.	0.86	.	.	.	-0.20	0.41
Gln	503	.	.	.	B	T	.	.	0.47	.	.	.	-0.20	0.74
Cys	504	.	.	B	B	.	.	.	0.11	.	*	.	-0.60	0.70

FIG. 4T

BNSDOCID <WO 0024756A1T1 >

SUBSTITUTE SHEET (RULE 26)

PATENT COOPERATION TREATY

REC'D 24 DEC 2001
WIPO PCT

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
4239-55911		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/26689	29/09/2000	02/10/1999
International Patent Classification (IPC) or national classification and IPC		
C07K14/00		
Applicant		
THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/04/2001	18.12.2001
Name and mailing address of the international preliminary examining authority: European Patent Office - Gitschiner Str. 103 D-10958 Berlin Tel. +49 30 25901 - 0 Fax: +49 30 25901 - 840	Authorized officer Siatou, E Telephone No. +49 30 25901 327

Form PCT IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/26689

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-71 as originally filed

Claims, No.:

1-41 as originally filed

Drawings, sheets:

1/8-8/8 as originally filed

Sequence listing part of the description, pages:

1-17, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

☐ the description, pages:

☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 1-26, 37-41 and 27-32(partially) in respect of industrial applicability.

because:

☒ the said international application, or the said claims Nos. 1-26, 37-41 and 27-32 (partially) in respect of industrial applicability relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 1-5, 17, 20-21, 23, 25-26, 33-38 (all partially).

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-22, 25-32, 40-41
	No:	Claims	1-6, 23-24, 33-39
Inventive step (IS)	Yes:	Claims	7-22, 25-32, 40-41
	No:	Claims	1-6, 23-24, 33-39
Industrial applicability (IA)	Yes:	Claims	27-32 (partially)
	No:	Claims	

2. Citations and explanations
see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. Claims 1-26, 27-32, as far as in vivo applications are conerned, and 37-41 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

2. An opinion will be given for those parts of the application which have been the subject of a search report, namely the parts relating to the use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunoreactive sensitized T cells sensitized with FGF-5.

.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The Applicant's attention is drawn to the fact that the present opinion expressed as to the novelty, inventive step and industrial applicability refers only to the matter for which an international search report has been drawn up.

Reference is made to the following documents:
D1: WO-A-9012597
D2: JP-A-10017599 (PAJ abstract)

Document D1 discloses pharmaceutical compositions comprising a conjugate of fibroblast growth factor (FGF) or a polypeptide reactive with an FGF receptor and a cytotoxic agent for treating a variety of FGF-mediated diseases, such as tumors. FGF-5 is explicitly mentioned (see claims 1-21 and page 5, lines 13-34). The subject matter of claims 1-6, 23-24 and 37-39 of the present invention is neither novel nor inventive (Art. 33(2) and 33(3) PCT).

Document D2 (see abstract) discloses antibodies binding exclusively to FGF-5 and

their use in detecting the presence of FGF-5. The subject matter of claims 33-36 is neither novel nor inventive (Art. 33(2) and 33(3) PCT).

None of the cited prior art documents discloses or suggests the subject matter of claims 7-22, 25-32 and 40-41. The subject matter of these claims meets the requirements of Art. 33(2) and 33(3) PCT.

Re Item VI

Certain documents cited

Certain published documents (Rule 70.10)

Application No Patent No (day/month/year)	Publication date (day/month/year)	Filing date (day/month/year)	Priority date (valid claim) (day/month/year)
WO-A-0024756	04.05.00	17.06.99	23.10.98
WO-A-9955861	04.11.99	15.04.99	28.04.98

Re Item VIII

Certain observations on the international application

Claim1 does not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. The claim attempts to define the subject-matter in terms of the result to be achieved which merely amounts to a statement of the underlying problem. The technical features necessary for achieving this result should be added.

Moreover, and as already stated in the search phase, support within the meaning of Art. 6 PCT and/or disclosure within the meaning of Art. 5 PCT is to be found for only a very small number of compounds/products within the scope of the present application, namely use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunoreactive sensitized T cells sensitized with FGF-5.

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Commissioner
US Department of Commerce
United States Patent and Trademark Office, PCT
2011 South Clark Place Room CP2/5C24
Arlington, VA 22202
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 17 July 2001 (17.07.01)	
International application No. PCT/US00/26689	**Applicant's or agent's file reference** 4239-55911
International filing date (day/month/year) 29 September 2000 (29.09.00)	**Priority date** (day/month/year) 02 October 1999 (02.10.99)
Applicant HANADA, Ken-Ichi et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

30 April 2001 (30.04.01)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer H. Zhou
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

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(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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12 April 2001 (12.04.2001)

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(10) International Publication Number
WO 01/25271 A3

(51) International Patent Classification⁷: A61K 38/18, C07K 14/50, A61K 39/395, C07K 16/22

(21) International Application Number: PCT/US00/26689

(22) International Filing Date:
29 September 2000 (29.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/157,103 2 October 1999 (02.10.1999) US

(71) Applicant *(for all designated States except US)*: **THE GOVERNMENT OF THE UNITED STATES OF AMERICA, as represented by THE SECRETARY, DEPARTMENT OF HEALTH AND HUMAN SERVICES** [US/US]; The National Institutes of Health, Office of Technology Transfer, Suite 325, 6011 Executive Boulevard, Rockville, MD 20852-3804 (US).

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(74) Agent: **NOONAN, William, D.**; Klarquist, Sparkman, Campbell, Leigh & Whinston, LLP, One World Trade Center, Suite 1600, 121 SW Salmon Street, Portland, OR 97204 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
with international search report

(88) Date of publication of the international search report:
10 May 2002

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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WO 01/25271 A3

(54) Title: FIBROBLAST GROWTH FACTOR-5 (FGF-5) IS A TUMOR ASSOCIATED T-CELL ANTIGEN

(57) Abstract: Disclosed herein are methods for treating tumors which express or over-express the tumor associated antigen (TAA) fibroblast growth factor 5 (FGF-5), including renal cell carcinoma (RCC) and carcinoma of the prostate and breast. Methods include modulating an immune response, such as increasing an immune response, or modulating FGF-5 expression or activity. The disclosure also includes methods of determining if a subject has an enhanced susceptibility to a disease associated with abnormal FGF-5 expression.

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INTERNATIONAL SEARCH REPORT

Internatic Application No
PCT/US 00/26689

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K38/18 C07K14/50 A61K39/395 C07K16/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	WO 00 24756 A (HUNAN GENOME SCIENCES INC.) 4 May 2000 (2000-05-04) claims 1-23 ---	1-41
X,P	WO 99 55861 A (EISAI CO. LTD.) 4 November 1999 (1999-11-04) claims 1-19,23,24 page 42, line 10 - line 3 page 46, line 20 -page 47, line 26 ---	1-5, 9-14,23, 24, 27-32, 37-40
X	WO 90 12597 A (THE SALK INSTITUTE FOR BIOLO) 1 November 1990 (1990-11-01) the whole document --- -/--	1-6,23, 24,37-39

[X] Further documents are listed in the continuation of box C

[X] Patent family members are listed in annex.

° Special categories of cited documents

"A" document defining the general state of the art which is not considered to be of particular relevance

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 July 2001	20/07/2001

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INTERNATIONAL SEARCH REPORT

Internatic Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication where appropriate, of the relevant passages	Relevant to claim No
X	PATENT ABSTRACTS OF JAPAN vol. 1998, no. 05, 30 April 1998 (1998-04-30) & JP 10 017599 A (POLA CHEM IND INC), 20 January 1998 (1998-01-20) abstract ---	33-36
A	ZHAN X ET AL: "THE HUMAN FGF-5 ONCOGENE ENCODES A NOVEL PROTEIN RELATED TO FIBROBLAST GROWTH FACTORS" MOLECULAR AND CELLULAR BIOLOGY,US,WASHINGTON, DC, vol. 8, no. 8, 1 August 1988 (1988-08-01), pages 3487-3495, XP002034597 ISSN: 0270-7306 abstract ---	1-41
A	DATABASE EMBASE 'Online! ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, NL; YAMANAKA K. ET AL: "Expression of fibroblast growth factors in human non-papillary renal cell carcinoma: Correlation with tumor progression." retrieved from STN Database accession no. 1999207619 XP002171451 abstract & INTERNATIONAL JOURNAL OF CLINICAL ONCOLOGY, (1999) 4/2 (74-77). , ---	1-41
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; YOSHIMURA, KOJI ET AL: "Messenger ribonucleic acids for fibroblast growth factors and their receptor in bladder and renal cell carcinoma cell lines" retrieved from STN Database accession no. 124:339650 HCA XP002171452 abstract & CANCER LETT. (SHANNON, IREL.) (1996), 103(1), 91-7 . --- -/--	1-41

INTERNATIONAL SEARCH REPORT

Internatic Application No
PCT/US 00/26689

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	DATABASE CHEMABS 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; WERNER, SABINE ET AL: "Fibroblast growth factor 5 proto-oncogene is expressed in normal human fibroblasts and induced by serum growth factors" retrieved from STN Database accession no. 116:35063 HCA XP002171453 abstract & ONCOGENE (1991), 6(11), 2137-44 , -----	1-41

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 1-26, 37-41 and 27-32, as far as they refer to an invivo method, are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Although claims 33-36 are directed to a diagnostic method practised on the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.2

Present claims 1-5, 17, 20-21, 23, 25-26, 33-38 relate to a compound defined by reference to a desirable characteristic or property, namely modulation of FGF-5 expression/activity or modulation of immune response to FGF-5.
The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the the use of FGF-5 polypeptides, nucleic acids encoding FGF-5, FGF-5 antisense molecules, antibodies to FGF-5 and immunorecative sensitezed T cells sensitized with FGF-5.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Int... ...ation on patent family members

Internatic Application No
PCT/US 00/26689

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